Notice of Allowability	Application No.	Applicant(s)	
	10/808,735	GIRARDIN ET AL.	
	Examiner	Art Unit	
	Robert A. Wax	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the election filed December 2, 2005*.

2. ☒ The allowed claim(s) is/are *1,3,4,6-16,20,21 and 24-37*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date 07202005
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *02212006* .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

DETAILED ACTION

Election/Restriction

1. After searching the elected invention the Examiner finds that a portion of the original restriction requirement is no longer applicable and is hereby modified. Groups I-III (except claims 14 and 17) are hereby rejoined with Groups VII-XIV. Claims 14 and 17 are moved into Group IV, along with claim 15. Thus, Claims 14-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on December 20, 2005.

Drawings

2. The drawings received on July 22, 2004 are accepted by the examiner.

EXAMINER'S AMENDMENT

3. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with William B. Raich on February 17, 2006.

The application has been amended as follows:

In the specification, paragraph [033], after, "Figure 1", insert - - -(a-d)- - -;

In paragraph [034], after, "Figure 2", insert - - -(a-f)- - -;

In paragraph [035], after, "Figure 3", insert - - -(a-e)- - -;

In paragraph [037], after, "Figure 5", insert - - -(a-c)- - -;

In paragraph [039], after, "Figure 7", insert - - -(a-b)- - -;

Replace the existing claim set with the following complete set of claims.

1. (currently amended) ~~A~~ An *in vitro* method for modulating Nod1 activity in a eukaryotic cell wherein said method comprises the steps of:

(a) expressing a functional Nod1 in a the eukaryotic cell; and

(b) bringing said cell into contact with a molecule ~~related to MTP~~ comprising:

(i) GlcNAc-MurNAc-L-Ala-D-Glu-mesoDAP (MTP);

(ii) MurNAc-L-Ala-D-Glu-mesoDAP;

(iii) L-Ala-D-Glu-mesoDAP; or

(iv) the molecule in which the L-Ala of (i), (ii), or (iii) is replaced with D-Ala.

2. (canceled)

3. (currently amended) The method of claim 1 ~~claim 2~~, wherein the molecule is ~~related to is the tripeptide~~ L-Ala-D-Glu-mesoDap or D-Ala-D-Glu-mesoDap ~~, a biologically active derivative thereof, or a peptidomimetic thereof~~.

4. (currently amended) The method of claim 1 ~~claim 2~~, wherein the molecule is ~~related to MTP is~~ GlcNAc-MurNAc-L-Ala-D-Glu-mesoDAP (MTP) or GlcNAc-MurNAc-D-Ala-D-Glu-mesoDAP~~, a biological derivative thereof, or a peptidomimetic thereof~~.

5. (canceled)

6. (currently amended) A method for modulating inflammation and/or apoptosis in a mammal due to Nod1 activity, wherein said method comprises administering a molecule ~~related to MTP~~ comprising:

(i) GlcNAc-MurNAc-L-Ala-D-Glu-mesoDAP (MTP);

(ii) MurNAc-L-Ala-D-Glu-mesoDAP;

(iii) L-Ala-D-Glu-mesoDAP; or

(iv) the molecule in which the L-Ala of (i), (ii), or (iii) is replaced with D-Ala

to said mammal.

7. (currently amended) The method of claim 6, wherein inflammation and/or apoptosis is increased ~~and the molecule related to MTP is a molecule which activity is agonist to the activity of MTP on Nod1~~.

8. (currently amended) The method of claim 6, wherein inflammation and/or apoptosis is decreased ~~and the molecule related to MTP is a molecule which activity is antagonist to the activity of MTP on Nod1~~.

9. (currently amended) A composition, which comprises a biologically acceptable carrier and ~~a biologically effective amount of~~ a molecule ~~related to MTP~~ comprising:

(i) GlcNAc-MurNAc-L-Ala-D-Glu-mesoDAP (MTP);

(ii) MurNAc-L-Ala-D-Glu-mesoDAP;

(iii) L-Ala-D-Glu-mesoDAP; or

(iv) the molecule in which the L-Ala of (i), (ii), or (iii) is replaced with D-Ala.

10. (currently amended) A compound, which is a tripeptide having the structure L-Ala-D-Glu-mesoDAP or D-Ala-D-Glu-mesoDap ~~, a biologically active derivative thereof, or a peptidomimetic thereof~~.

11. (currently amended) A compound for increasing *in vivo* inflammation and/or apoptosis due to Nod1 activity or useful as an adjuvant agent in eukaryotes, wherein said compound is a tripeptide having the structure L-Ala-D-Glu-mesoDAP or D-Ala-D-Glu-mesoDap ~~, a biologically active derivative thereof, or a peptidomimetic~~

~~thereof, and wherein when said compound is used as an adjuvant agent,~~ and wherein the amino acid Ala of said tripeptide is not linked to a N-acylmuramic acid.

12. (currently amended) The compound ~~molecule~~ of claim 11 for use as an adjuvant.

13. (currently amended) A composition~~, which comprises~~ comprising an antigen and the compound of claim 12 in an amount effective to increase *in vivo* inflammation and/or apoptosis due to Nod1 activity ~~a biologically effective amount of the molecule of claim 12~~.

14-19. (canceled)

20. (currently amended) A method for detecting the dysfunction of a molecule of an ~~the~~ inflammatory and/or apoptosis pathway in which Nod1 is involved wherein said method comprises the steps of:

(a) providing a cell in which the dysfunction of a molecule of the inflammatory and/or apoptosis pathway in which Nod1 is involved, is suspected,

(b) bringing said cell into contact with ~~MTP or an agonist thereof,~~ a test molecule comprising:

(i) GlcNAc-MurNAc-L-Ala-D-Glu-mesoDAP (MTP);

(ii) MurNAc-L-Ala-D-Glu-mesoDAP;

(iii) L-Ala-D-Glu-mesoDAP; or

(iv) the test molecule in which the L-Ala of (i), (ii), or (iii) is replaced with D-Ala;

(c) evaluating NF-κB activation or IL-8 production

wherein an altered activation of NF-κB or an altered production of IL-8 is indicative of a dysfunction of a the molecule of the inflammatory and/or apoptosis pathway in which Nod1 is involved.

21. (currently amended) A method for screening for a molecule which is capable of modulating an inflammatory and/or apoptotic response obtained after direct or indirect interaction between Nod1 and MTP, wherein said method comprises the steps of :

(a) providing a cell expressing a functional Nod1;

(b) bringing said cell into contact with the molecule to be tested;

(c) measuring the activation of NF-κB and/or the production of IL-8;

and optionally

(d) comparing the result of step c) with a result obtained in absence of the molecule to be tested;

wherein the altered NF-κB activation and/or IL-8 production compared to NF-κB activation and/or IL-8 production in the absence of the molecule to be tested is indicative of the capability of the tested molecule to modulate an inflammatory response resulting from the infection of a mammal a Gram-negative bacteria.

22-23. (canceled)

24. (currently amended) A peptidic complex containing Nod1 and ~~MTP or a derivative or a peptidomimetic thereof~~ a molecule comprising:

(i) GlcNAc-MurNAc-L-Ala-D-Glu-mesoDAP (MTP);

(ii) MurNAc-L-Ala-D-Glu-mesoDAP;

(iii) L-Ala-D-Glu-mesoDAP; or

(iv) the molecule in which the L-Ala of (i), (ii), or (iii) is replaced with D-Ala.

25. (currently amended) The composition of claim 9 for ~~preventing or~~ treating a Gram-negative bacterial infection.

26. (original) A method for the detection of peptidoglycan from a Gram-negative bacteria in a sample, wherein the method comprises:

a) providing a sample in which peptidoglycan is to be detected;

b) bringing said sample into contact with Nod1 protein;

c) detecting an interaction between MTP and Nod1;

wherein an interaction between MTP and Nod1 is indicative of the presence of peptidoglycan from Gram-negative bacteria in the sample.

27. (original) The method of claim 26, wherein interaction between MTP and Nod1 is detected by measuring NF-κB activation.

28. (original) The method of claim 26, wherein interaction between MTP and Nod1 is detected by a bioluminescent signal.

29. (original) The method of claim 28, wherein said bioluminescent signal is obtained by means of FRET technology.

30. (currently amended) A method for the detection of peptidoglycan in a sample and optionally determining the Gram-negative or Gram-positive bacterial origin of said peptidoglycan, wherein the method comprises:

a) providing a sample in which peptidoglycan is to be detected;

b) bringing said sample into contact with Nod1 protein and with Nod2 protein;

c) detecting an interaction between MTP and muramyl dipeptide (MDP) ~~MDP~~ and at least one of the two Nod proteins, and optionally;

d) distinguishing between the interaction with Nod1 from the interaction with Nod2;

wherein an interaction with at least one of the two Nod proteins in c) is indicative of the presence of peptidoglycan in the sample and wherein an interaction with only Nod2 in d) is indicative of a peptidoglycan of Gram-positive bacterial origin in

the sample while an interaction with Nod1 and Nod2 is indicative of a peptidoglycan of Gram-negative bacterial origin in the sample.

31. (original) The method of claim 30, wherein interaction between MTP or MDP and Nod proteins is detected by measuring NF-κB activation.

32. (original) The method of claim 30, wherein interaction between MTP or MDP with Nod proteins is detected by a bioluminescent signal.

33. (original) The method of claim 32, wherein said bioluminescent signal is obtained by means of FRET technology.

34. (currently amended) A method for screening for a molecule that modulates interaction between Gram-negative bacteria peptidoglycan and Nod1, wherein said method comprises:

a) providing MTP;

b) bringing said MTP into contact with Nod 1 protein in the presence and in the absence of the tested molecule;

c) evaluating the interaction between MTP and Nod1 in the presence and in the absence of the tested molecule;

wherein a modulation of the interaction between MTP and Nod1 in the presence of the tested molecule indicates that said molecule modulates said interaction between Nod1 and Gram-negative bacteria peptidoglycan.

36. (new) The method of claim 1, wherein the molecule is MurNAc-L-Ala-D-Glu-mesoDAP or MurNAc-D-Ala-D-Glu-mesoDAP.

37. (new) The method of claim 1, wherein Nod1 activity is detected by measuring NF-κB activation.

4. The following is an examiner's statement of reasons for allowance: A careful search of the prior art reveals no previously known connection between Nod proteins and MTP; furthermore, search of the compound L-Ala-D-Glu-mesoDAP in the CAS Registry file revealed the novelty of the compound.

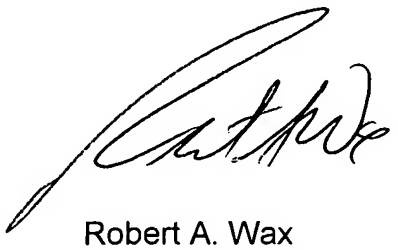
Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Wax whose telephone number is (571) 272-

0623. The examiner can normally be reached on Monday through Friday, between 9:00 AM and 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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